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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/823,356	03/30/2001	Y. Tom Tang	PF-0489-1 CON	9453

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INCYTE CORPORATION (formerly known as Incyte Genomics, Inc.)
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EXAMINER
MURPHY, JOSEPH F

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/823,356	TANG ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,9,11-16,27,28 and 79-83* is/are pending in the application.

4a) Of the above claim(s) *1,2,13-16,27,28,81 and 82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,5-7,9,11,12,79,80 and 83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Formal Matters

Claim 4 was cancelled, and claim 11 was amended, in Paper No. 13, 12/20/2003. Claims 1-3, 5-7, 9, 11-16, 27-28, 79-83 are pending. Claims 1-2, 13-16, 27-28, 81-82 stand withdrawn from consideration pursuant to 37 CFR 1.142(b). Claims 3, 5-7, 9, 11-12, 79-80, 83 are under consideration.

Declaration

The Declaration under 37 CFR 1.132 filed in Paper No. 15, 4/28/2003 is insufficient to overcome the rejection of claims 3-7, 9, 11-12, 79-80 based upon 35 USC 101 and 112 first paragraph as set forth in the last Office action for the reasons set forth below

Response to Amendment

Applicant's arguments filed in Paper NO. 15, 4/28/2003 have been fully considered but they are not persuasive, for the reasons set forth below.

The rejection of claim 11 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,691,147 (Draetta et al.) has been obviated by Applicant's amendment and is thus withdrawn.

Claim Rejections - 35 USC §§ 101, 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-7, 9, 11-12, 79-80 stand rejected, and new claim 83 is rejected, under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed patentable utility. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby, for reasons of record set forth in Paper NO. 10, 2002. The instant application does not disclose the biological role of this protein or its significance. The claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well-established utility and must undergo extensive experimentation. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

The rejection of record set forth that it is clear from the instant specification that the nucleic acid encoding the MSP-9 polypeptide has been assigned a function because of its similarity to known proteins (Specification at 30, line 4). However, it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors (Doerks et al.1998). These errors can be due to sequence similarity of the query region to a region of the alleged similar protein that is not the active site, as well as homologs that did not have the same catalytic activity because active site residues of the characterized family were not conserved (Doerks et al. page 248, column 3, fourth and fifth paragraphs). Inaccurate use of sequence-to-function methods have led to significant function-annotation errors in the sequence databases (Doerks et al. page 250, column 1, third paragraph). Furthermore, Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al.

(1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

After complete characterization, this protein may be found to have a patentable utility. This further characterization, however, is part of the act of invention and until it has been undertaken Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson,* 148 USPQ 689 (Sup. Ct., 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 USC § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to a nucleic acid encoding a polypeptide which has an as yet undetermined function or biological significance. Until some actual and specific significance

can be attributed to the protein identified in the specification as MSP-9, the instant invention is incomplete. The polypeptide encoded by the nucleic acids of the instant invention is alleged to be structurally analogous to a protein that is known in the art as the IL-1 receptor intracellular domain ligand. In the absence of knowledge of the biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which inhibit its activity is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real world" use for MSP-9 then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 USC § 101 as being useful.

Claims 3-7, 9, 11-12, 79-80 stand rejected, and new claim 83 is rejected, under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant argues that the use of the claimed polynucleotide for toxicology testing, drug discovery and disease diagnosis is a specific, substantial and credible real world utility. According to MPEP § 2107, a rejection for lack of utility is imposed when an invention lacks an asserted specific and substantial utility for the claimed invention and it does not have a readily apparent well-established utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible. In the instant case, the preponderance of the

evidence indicates that a person of ordinary skill in the art would not immediately appreciate why the invention is useful based on the characteristics of the invention, for the reasons set forth above, and further, that the claimed invention lacks a specific or substantial utility. Thus the *prima facie* showing of no utility has been made.

With regard to drug discovery and development, (Dec. at ¶14) Applicant mentions expression profiling as one use of the claimed polypeptide in the instant application. Applicant states expression profiling is a method for identifying drug targets and to characterize diseases, and cites Rockett et al. to show that a pattern of gene changes may be correlated to the unknown compound, and further cites Lashkari et al. to show that amplicons can be arrayed onto glass for expression analysis. Such a profile is independent of the function of the genes or gene products. In the instant case, the claimed polynucleotide and polypeptide can be used as one of many targets on a microarray to generate an expression profile. A transcript image thus generated from lung tumor tissue can be compared, for example, with that from lung tumor tissue treated with a potential therapeutic compound in order to evaluate the efficacy of the compound. However, there is no way to assess the meaning of any individual hit obtained from this procedure. The first requirement is that one must know the biological significance of the polypeptide that is being evaluated. Without this information, the results of the expression profile does not have specific and substantial use because one would not know if the polypeptide expression should be increased or decreased or even what significance could be attributed to such changes in expression profiles.

Applicant further argues, citing the Bedilion Declaration (Dec. at ¶3) the utility of the claimed polypeptide in the diagnosis of disease. However, in order for a polynucleotide

encoding a polypeptide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polypeptide and a disease or disorder. The presence of a polypeptide in tissue that is derived from cancer cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed polypeptide and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polypeptide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polypeptide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polypeptide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polypeptide and any disease or disorder and the lack of any correlation between the claimed polypeptide with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. Congress intended that no patent be granted on a chemical compound whose sole utility consists of its potential role as an object of use-testing. *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. § 101.

Applicant further argues, citing the Bedilion Declaration (Dec. at ¶6) that selectivity screening is a well-established utility and concludes that the claimed polypeptides could be used in this manner and that the claimed invention possesses utility. However, for a utility to be

"well-established" it must be specific, substantial and credible. In this case all nucleic acids and genes are in some combination useful in selectivity screening. However, the particulars of selectivity screening with a p0lynucleotdie of SEQ ID NO: 26, or the polypeptide of SEQ ID NO: 9, are not disclosed in the instant specification. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to SEQ ID NO: 26. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polypeptide in an array for selectivity screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility that would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicant's individual polypeptide is affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polypeptide has no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what use any expression information regarding the polynucleotide or polypeptide could be put.

Applicant further alleges that the uncontested fact that the claimed polynucleotide encodes a membrane spanning protein also demonstrates utility. However, the Doerks reference was cited to show that it is commonly known in the art that sequence-to-function methods of

assigning protein function are prone to errors. Doerks discuses several proteins which have had their function predicted based on homology to known proteins, for example, an assignment error was made for proteins gil2314657 and gil2688341 based on significant similarity to proline dipeptidases, when this assignment was based on similarity of a region that was not the active site (page 248 column 3, third full paragraph). The Brenner reference was cited to show that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Thus, based on the teachings of Doerks, Brenner and Bork, the determination of a function for an encoded polypeptide based on sequence data is difficult and does not provide a well-established utility for the claimed polypeptide and polynucleotide.

The rejection of record further set forth that even if, *arguendo*, the nucleic acid of the instant invention is found to have a patentable utility, claims 3-7, 9, 11-12, 79-80 stand rejected, and new claim 83 is rejected, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding an amino acid of SEQ ID NO: 9, or a nucleic acid with the sequence as set forth in SEQ ID NO: 26, does not reasonably provide enablement for a nucleic acid which is 90% identical to SEQ ID NO: 26, for reason of record set forth in Paper No. 10, 9/26/2002. The specification does not enable any person skilled in the art to which

it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 3-7, 9, 11-12, 79-80 are overly broad since insufficient guidance is provided as to which of the myriad of variant nucleic acids encode polypeptides which will retain the characteristics of MSP-9. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of MSP-9. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

Since the claims encompass variant nucleic acids and polypeptides and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The claims as written do not set forth a functional limitation for the polynucleotides are encoded polypeptides encompassed by the claims. Since the amino acid sequence of a polypeptide determines its structural and functional

properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims.

Applicant argues that the specification sets forth that polynucleotide variants and encoded polypeptide variants can be constructed and then tested for functionality. However, Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polynucleotides and encoded polypeptides which the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed polynucleotides and encoded polypeptides, since the skilled artisan would have to first make polypeptide variants, but there is no functional limitation set forth for the claimed encoded polypeptides. Thus, since Applicant has only taught how to test for polynucleotide and polypeptide variants of MSP-9, and has not taught how to make polynucleotide and polypeptide variants of MSP-9, it would require undue experimentation of one of skill in the art to make and use the claimed method.

Applicant argues that since the claims are drawn to naturally occurring sequences, one of skill in the art would only need to screen a cDNA library or use appropriate PCR conditions to make the claimed polynucleotides and polypeptides. However, the term naturally occurring is indefinite as set forth in the rejection under 35 USC § 112 second paragraph, infra. Additionally, as set forth in the Written Description rejection, to the extent that the claims encompass naturally occurring sequences they contain. The specification fails to identify and describe regions essential to the

function of the claimed invention, such as the untranslated regions, introns, and promoter sequences which are required since the invention encompasses naturally occurring sequences. Therefore, the structure of these elements is not conventional in the art and one of skill in the art would not recognize from the disclosure that applicant was in possession of the genus of nucleic acids encompassed by the claimed invention. Additionally, Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polynucleotides and polypeptides that the specification only teaches one skilled in the art to test for functional variants. Since the claims do not enable one of skill in the art to make and use the claimed polynucleotides and polypeptides, but only teaches how to screen for the claimed polynucleotides and polypeptides, and since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims.

Claims 3-7, 9, 11-12, 79-80 stand rejected, and new claim 83 is rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in paper NO. 10, 9/26, 2002. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

These are genus claims. The claims are drawn to a nucleic acid which encodes a naturally occurring n amino acid sequence which is 90% identical to SEQ ID NO: 9. The

specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the encoded SEQ ID NO: 26. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a nucleic acid with a sequence as set forth in SEQ ID NO: 9, and the polypeptide of SEQ ID NO: 26 is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Applicant argues that since the subject matter of the claims is defined in terms of the chemical formula of SEQ ID NO: 9 and 26, and there is no reliance merely on the description of functional characteristics of the claimed polynucleotides and polypeptides, the claims meet the written description standard. Applicant further argues that the claims do not describe a highly variant genus. However, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction

to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polynucleotides and encoded polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. in the instant case, there is no functional limitation set forth for the encompassed polynucleotide and polypeptide variants. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed: there is no guidance in the art as to what the defining characteristics of the polypeptides might be since no functional limitation is set forth. Additionally, the term naturally occurring is indefinite as set forth in the rejection under 35 USC § 112 second paragraph, infra. Additionally, to the extent that the claims encompass naturally occurring sequences they contain. The specification fails to identify and describe regions essential to the function of the claimed invention, such as the untranslated regions, introns, and promoter sequences which are required since the invention encompasses naturally occurring sequences. Therefore, the structure of these elements is not conventional in the art and one of skill in the art

would not recognize from the disclosure that applicant was in possession of the genus of nucleic acids encompassed by the claimed invention.

Thus, no identifying characteristics or properties of the instant polynucleotide s and polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a host cell in culture comprising a polynucleotide with the sequence as set forth in SEQ ID NO: 26, does not reasonably provide enablement for in vivo transfection, for reasons of record set forth in Paper No. 10, 9/26/2002.

The specification discloses that the nucleic acids of the current invention can be expressed in a wide variety of host cell types, including animal cell systems (Specification at 40, line 15-21) and in vivo (Specification at 52, lines 26-30). However, there are no actual or prophetic examples that disclose how to make or use host cells that comprise a DNA sequence as set forth in SEQ ID NO: 26 in an animal. The Examiner cites Eck & Wilson (page 81, column 2, second paragraph to page 82, column 1, second paragraph) who report that numerous factors complicate *in vivo* gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the

genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. Since the instant disclosure does not address any of the methods necessary to make a host cell in an animal that comprises the polynucleotide of interest, the claim as written is not enabled.

Applicant argues that the claims do not need to be enabled for transfection of host cells in an animal, since the claims are enabled for host cells in culture, and that one of skill in the art would routinely be able to make a host cell in an animal. While the claims are enabled for a host cell in culture comprising the polynucleotide of SEQ ID NO: 26, and cells isolated from a transgenic animal which comprise the polynucleotide of SEQ ID NO: 26, the claims are not enabled for host cells within an animal that comprise the polynucleotide of SEQ IDNO: 26. it would require undue experimentation for one of skill in the art to detect which cells within the animal were transformed with the polynucleotide.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-7, 9, 11-12, 79-80 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record set forth in Paper No. 10, 9/26/2002.

Claims 3, 11 and 12 are indefinite in the recitation of the term "naturally occurring". It is unclear whether this term imposes a required limitation on the claim, such that it only encompasses, for example, polynucleotides amplified from human cDNA, or only sequences produced by digestion with restriction enzymes of DNA isolated from tissue that contains polynucleotides encoding the polypeptide, or if the claim encompasses all polynucleotide sequences that encode the polypeptide. Therefore, the metes and bounds of the claim are unclear. Claims 4-9, 79-80 are rejected due to their dependence on claims 3, 11 and 12.

Applicant argues that the term naturally occurring is not a limitation on the claimed polynucleotides and polypeptides, and that it would be recognized by one of skill in the art to encompass sequences which occur in nature. In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph "by providing clear warning to others as to what constitutes infringement of the patent". See, e.g., Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). MPEP 2173.02, MPEP 2173.02. In the instant case, the fact that Applicant argues that it is not a limitation on the encompassed polynucleotides and polypeptides, but that the use of the term imparts some information to one of skill in the art underscores the indefinite nature of the language. Does a polynucleotide or polypeptide, in order to be considered naturally occurring, have to be amplified from human cDNA, or produced by digestion with restriction enzymes of DNA isolated from tissue that contains polynucleotides encoding the polypeptide, or does the term encompass sequences which are homologous to sequences found in nature? Or is it not a

limitation at all, in which case no information regarding the scope of the claim is added? The use of this language clearly does not provide clear warning to others as to what constitutes infringement of the patent, and thus does not meet the requirements of 35 USC 112 second paragraph.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
September 9, 2003

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600